KP- 1461

Drug Class: **Nucleoside Reverse Transcriptase Inhibitors**

Drug Description

KP-1461 is a potent, nonchain-terminating, mutagenic deoxyribonucleoside analogue. Designated a DNA covert nucleoside, the drug consists of a modified base that incorporates randomly into HIV and pairs with multiple bases. [1] [2] [3]

HIV/AIDS-Related Uses

KP-1461, also known as SN1461, is entering Phase Ib trials for the treatment of HIV-1 infection in adults.[4] [5] KP-1461 has antiviral activity against both HIV-1 and HIV-2.[6]

Pharmacology

KP-1461 is the oral prodrug of KP-1212. KP-1461 is also known as SN1212.[7] bKP-1461 introduces continual mutations into HIV during viral replication by reverse transcriptase (RT). These mutations decrease virus viability and are eventually lethal. This mechanism, selective viral mutagenesis or lethal mutagenesis, is novel to the nucleoside analogue class.[8]

Unlike approved nucleoside RT inhibitors (NRTIs) that contain a modified sugar and unmodified base, KP-1461 has a modified base that allows multiple base pairing. Because KP-1461 pairs with multiple bases, it is able to target all viral proteins rather than a single protein.[9] [10]

KP-1461, after conversion to KP-1212, is metabolized to a triphosphate and incorporated into the HIV-1 genome by RT. The drug is similarly incorporated into human mitochondrial DNA polymerase.[11] The active substance KP-1212 has been shown to inhibit antiviral activity in tissues after just one pass; accumulation has been shown to eradicate the virus entirely.[12] HIV strains treated with KP-1212 also showed increased sensitivity to zidovudine.[13]

In laboratory tests, multiple tissue passes failed to induce resistant HIV isolates after several attempts.[14] No cross resistance has been observed with HIV strains resistant to common nucleoside analogues such as zidovudine, lamivudine, stavudine, and abacavir.[15]

Adverse Events/Toxicity

No significant genotoxicity was observed in vitro in Chinese hamster ovary cells or in human B cells.[16] At doses up to 2 g/kg, no toxicity was observed in dogs; lactate levels did not increase, reflecting a lack of mitochondrial toxicity.[17] KP-1461 lacked consistent, dose-related toxicities and did not appear harmful to humans in an early Phase Ia study.[18]

Clinical Trials

For information on clinical trials that involve KP-1461, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: KP-1461 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[19]

Other Names

SN1461[20]

SN1212 [metabolized drug][21]

KP-1212 [metabolized drug][22]

KP-1212/1461[23]

Further Reading

Study of Nucleoside Analog for the Treatment of HIV Positive Patients Who Have Failed Multiple HAART Regimens. ClinicalTrials.gov. Available at:

Further Reading (cont.)

Harris K, Brabant B, Li L, Styrchak S, Gall A, Daifuku R. SN1212/1461 a Novel Mutagenic Deoxyribonucleoside Analog with Activity Against HIV. San Francisco, Abstract 532, 2004.

Harris KS, Brabant W, Styrchak S, Gall A, Daifuku R. KP-1212/1461, a nucleoside designed for the treatment of HIV by viral mutagenesis. Antiviral Res. 2005 Jul;67(1):1-9. PMID: 15890415

Murakami E, Basavapathruni A, Bradley WD, Anderson KS. Mechanism of action of a novel viral mutagenic covert nucleotide: molecular interactions with HIV-1 reverse transcriptase and host cell DNA polymerases. Antiviral Res. 2005 Jul;67(1):10-7. Epub 2005 Jan 26. PMID: 15950748

Manufacturer Information

KP-1461
Koronis Pharmaceuticals
12277 134th Court NE, Suite 110
Redmond, WA 98052
(425) 825-0240

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

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22. Antiviral Res - Jul;67(1):10-7. Epub 2005 Jan 26.

23. Antiviral Res - 2005 Jul;67(1):1-9